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A Convenient Synthesis of $\Delta^{7,8}$-Morphinan-6-one and Its Direct Oxidation to 14-Hydroxy-$\Delta^{7,8}$-morphinan-6-one

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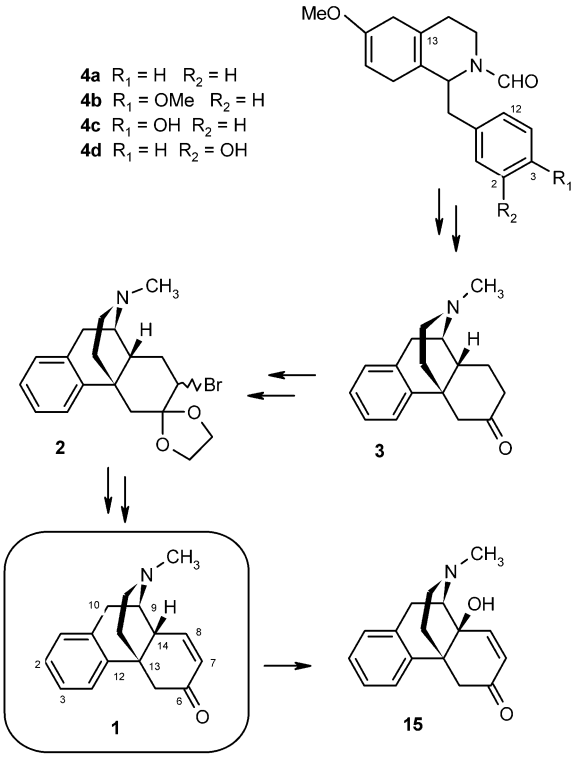
Abstract—Synthesis of $\Delta^{7,8}$-morphinan-6-one by Grewe cyclization and bromoketalization reaction as crucial steps is described. Introduction of a hydroxyl group at 14-position is demonstrated by direct oxidation with MnO_2 in the presence of silica gel.

With increasing knowledge about agonistic and antagonistic activities of morphinan derivatives at opioid receptors,[1] the field of potential application for this class of compounds is broadening and the demand of novel procedures to obtain new analogues is rising.[2]

In this context, compounds containing the $\Delta^{7,8}$ double bond offer the possibility for further manipulations such as the stereoselective introduction of a hydroxyl group at C14[3] in the search for novel agonist and antagonists ligands possessing opioid receptor affinity. $\Delta^{7,8}$-Morphinanones and 14-hydroxymorphinanones generally derive from thebaine, the common starting material that has only a low natural abundance.

As part of our program directed toward the synthesis of nitrogen containing compounds with interesting pharmacological activity, we present here a convenient synthesis of 7,8-didehydro-6-morphinanone **1** as depicted in Scheme 1 where the crucial steps are the Grewe cyclization[4] of an appropriate hexahydroisoquinoline for the construction of the tetracyclic skeleton and a bromoketalization for the creation of the unsaturated ketone.[5]



Scheme 1.

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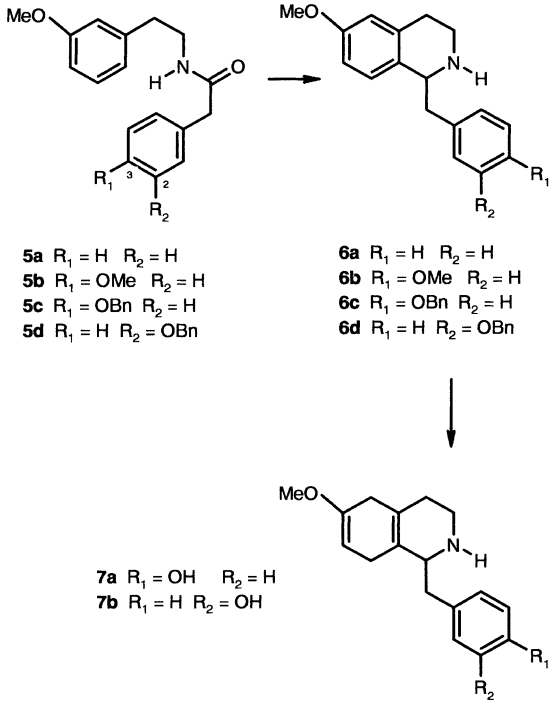
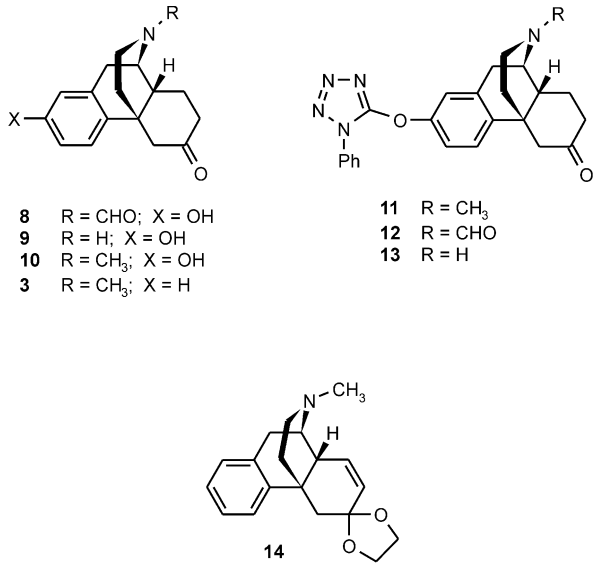


Scheme 2.



Scheme 3.

The first retrosynthetic analysis identified as ideal substrate for the Grewe cyclization the hexahydroisoquinoline **4a** that we planned to obtain by Birch reduction of the corresponding tetrahydroisoquinoline **6a**[6] (Scheme 2).

The submission of **6a** to Birch conditions (Li, NH_3, THF–*t*BuOH 1:1, −78 °C) caused the undesired reduction of both phenyl rings.

In order to reduce the susceptibility of reduction in the second phenyl ring we introduced an electron-rich substituent on position 3 (for the sake of simplicity we use for the intermediates the numbering system of the target morphinan skeleton).

The first choice was the methoxy group, but when compound **6b**[7] was submitted to Birch conditions we observed again reduction of both phenyl rings. We then moved to the preparation of compound **6c** that by Birch reduction gave the desired hexahydroisoquinoline **7a**.[8] Reaction of **7a** with HCOOEt in DMF at 80 °C gave compound **4c** (95% yields). Our efforts to induce Grewe cyclization of compound **4c** with 80% sulfuric at 25 °C or orthophosphoric acid at 135 °C were unsuccessful even though examples of this type are reported in the literature.[8]

We reasoned that position 12 was not sufficiently activated by the presence of OH group at position 3, and for this reason we supposed a successful reaction when the OH group was at position 2. The condensation reaction of 3-methoxyphenylethylamine and 3-benzyloxyphenylacetic acid[9] was maintained at 200 °C for 5 h to give the amide **5d** (80%) that was submitted to Bischler–Napieralski cyclization in CH_2Cl_2 with PCl_5 at room temperature. After one night, the addition of $EtOH/Et_2O$ allowed to obtain a white solid of the iminium chloride salt (yield 67%) that was converted to the tetrahydroisoquinoline **6d** by reduction with $NaBH_4$ in MeOH (yield 97%). The Birch reaction (Li, NH_3, THF–tBuOH 1:1, −78 °C) occurred at the methoxy substituted phenyl ring, as expected, and was accompanied by hydrogenolysis of the benzyloxy group to give compound **7b** (95% yield). Subsequent reaction of **7b** with HCOOEt in DMF at 80 °C gave compound **4d** (95% yield).

The Grewe cyclization of derivative **4d** (80% sulfuric acid and Et_2O at 25 °C) proceeded with *trans* addition to the double bond with the smoothly formation of C12–C13 bond and afforded the *N*-formyl-2-hydroxy-6-morphinanone **8** (82% yield)[10] (Scheme 3).

Compound **8** was submitted to hydrolysis of formyl group (HCl, MeOH, 70 °C) to give **9** (96% yield). The subsequent reductive *N*-methylation with formaldehyde in the presence of Pd/C gave compound **10** (40% yield) that by introduction of 5-chloro-1-phenyl-1*H*-tetrazole, (K_2CO_3, DMF, rt) gave the corresponding derivative **11** (65% yield). Hydrogenation reaction of **11** in formic acid in the presence of Pd/C gave the expected compound **3** (74% yield).[10b, 11] It was possible to change the order of the described steps to obtain compound **11**. We achieved the introduction of the phenyltetrazole on the *N*-formylated compound using the same conditions described to give **12** (50% yield). The hydrolysis of the formyl group (85% yield) gave **13**. Compound **11** was obtained by reductive methylation of **13** (59% yield).

This alternative preparation presents similar total yield as the first sequence (**8**–**9**–**10**–**11**) but several chromatographic purifications are required. The next goal in our plan was the introduction of $\Delta^{7,8}$ double bond, a task that was accomplished by a sequence of reactions starting with a bromoketalization step that proceeded regioselectively to give **2**[12] as a mixture of diastereoisomers

(dry ethylene glycol, bromine, 70 °C, 50% yield).[13] The dehydrobromination of α-bromo ketal **2** with DBU in DMSO failed to give the desired product thus the use of *t*BuOK in DMSO at 85 °C was preferred.[14] The resulting compound **14** was reacted with 3 N HCl in MeOH (reflux) to provide the enone **1** (yield 87%).[15]

The availability of compound **1** gave us the opportunity to study the oxidation to 14-hydroxy derivative. This reaction has been described, on morphine related derivatives, using a variety of two-steps procedures via formation of a diene system followed by oxidation.[16]

We preferred a direct procedure that offers the advantage of less synthetic steps and overcomes the necessity for the isolation of a diene intermediate. The use of MnO_2 as oxidant in the presence of silica gel afforded the stereoselective introduction of the hydroxyl group at position C14.[3,17]

To confirm the structure of the obtained compound **15** the ^{1}H NMR signal of H-8 appeared at δ 5.69 as doublet ($J = 10$ Hz) while in the starting compound it appeared as doublet of doublet (δ 5.73, $J = 10$, 3 Hz).

In summary, we have developed a practical synthesis of 7,8-didehydro-6-morphinanone **1** with a high-yield sequence of reactions and the first direct oxidation at C14 of a morphinan compound. The insertion of a hydroxyl group into the 14-position of morphine like structures, generally gives compounds with interesting pharmacological activity;[1] for this reason, compound **15** encourages its use as a suitable synthon for the preparation of new pharmacologically active compounds.

Acknowledgement

The authors would like to thank GlaxoSmithKline S.p.A Milano (Italy) for financial support.

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15. 7,8-Didehydro-6-morphinanone **1**: ^{1}H NMR (DMSO-d_6) δ 7.25–7.05 (4H, m, ArH), 6.90 (1H, bd, $J = 10$ Hz, H-7), 5.73 (1H, dd, $J = 10$, 3 Hz; H-8), 2.35 (3H, s, N–Me), 3.40–1.80 (10H, m).
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17. A suspension of compound **1** (68 mg, 0.27 mmol) and MnO_2 (680 mg) in CH_2Cl_2 (10 mL) was stirred for 1 day at 40 °C. When the disappearance of starting compound was complete silica-gel (200 mg, Merck, 60H) was added and the stirring was maintained for 1 day at 40 °C. The mixture was filtered and the residue was washed with CH_2Cl_2 containing 1% of MeOH. Evaporation gave the title compound. 7,8-Didehydro-14-hydroxy-6-morphinanone **15** (yield 59%): ^{1}H NMR ($CDCl_3$) diagnostic signals δ 7.35–7.00 (4H, m, ArH), 6.61 (1H, bd, $J = 10$ Hz, H-7), 5.69 (1H, d, $J = 10$, Hz; H-8). Low EIMS: 269 (M^+).